Long-term Use of Aspirin and Age-Related Macular Degeneration

Barbara E. K. Klein, MD, MPH
Kerri P. Howard, MS
Ronald E. Gangnon, PhD
Jennifer O. Dreyer, BS
Kristine E. Lee, MS
Ronald Klein, MD, MPH

Context Aspirin is widely used for relief of pain and for cardioprotective effects. Its use is of concern to ophthalmologists when ocular surgery is being considered and also in the presence of age-related macular degeneration (AMD).

Objective To examine the association of regular aspirin use with incidence of AMD.

Design, Setting, and Participants The Beaver Dam Eye Study, a longitudinal population-based study of age-related eye diseases conducted in Wisconsin. Examinations were performed every 5 years over a 20-year period (1988-1990 through 2008-2010). Study participants (N=4926) were aged 43 to 86 years at the baseline examination. At subsequent examinations, participants were asked if they had regularly used aspirin at least twice a week for more than 3 months.

Main Outcome Measure Incidence of early AMD, late AMD, and 2 subtypes of late AMD (neovascular AMD and pure geographic atrophy), assessed in retinal photographs according to the Wisconsin Age-Related Maculopathy Grading System.

Results The median duration of follow-up was 14.8 years. There were 512 incident cases of early AMD (of 6243 person-visits at risk) and 117 incident cases of late AMD (of 8621 person-visits at risk) over the course of the study. Regular aspirin use 10 years prior to retinal examination was associated with late AMD (hazard ratio [HR], 1.63 [95% CI, 1.01-2.63]; $P=.05$), with estimated incidence of 1.76% (95% CI, 1.17%-2.64%) in regular users and 1.03% (95% CI, 0.70%-1.51%) in nonusers. For subtypes of late AMD, regular aspirin use 10 years prior to retinal examination was significantly associated with neovascular AMD (HR, 2.20 [95% CI, 1.20-4.15]; $P=.01$) but not pure geographic atrophy (HR, 0.66 [95% CI, 0.25-1.95]; $P=.45$). Aspirin use 5 years (HR, 0.86 [95% CI, 0.71-1.05]; $P=.13$) or 10 years (HR, 0.86 [95% CI, 0.65-1.13]; $P=.28$) prior to retinal examination was not associated with incident early AMD.

Conclusions Among an adult cohort, aspirin use 5 years prior to observed incidence was not associated with incident early or late AMD. However, regular aspirin use 10 years prior was associated with a small but statistically significant increase in the risk of incident late and neovascular AMD.

JAMA. 2012;308(23):2469-2478 www.jama.com

Aspirin use in the United States is widespread, with an estimated 19.3% of adults reporting regular consumption, and reported use increases with age.[1] Aspirin is used for temporary relief of pain and for arthritic or rheumatologic diseases[2] and for its antipyretic effects. It is considered a nonsteroidal anti-inflammatory drug (NSAID), but it also suppresses thromboxanes by inactivation of cyclooxygenase, thus impairing the clot-enhancing action of platelets. This has made it attractive as a medical intervention for acute myocardial infarction; about half of persons who were told that they have heart disease reported taking aspirin every day or every other day.[1]

The results of cross-sectional studies of aspirin use and its relation to age-related macular degeneration (AMD) have been inconsistent.[3-5] AMD is a potentially blinding condition for which prevalence and incidence are increasing with the increased survival of the population, and regular use of aspirin is common and becoming more widespread in persons in the age range at highest risk for this disease. Therefore, it is imperative to further examine this potential association. The Beaver Dam Eye Study, a longitudinal study of age-related eye diseases, has assessed an adult population (aged 43 to 86 years at baseline) at 5-year intervals over a 20-year period. This study provided the unique opportunity to investigate the link between AMD and aspirin use in a population which, by virtue of its age distribution and low attrition, permitted examination of the associations of aspirin use 5 and 10 years before observed AMD incidence.

METHODS

Participants

A private census of Beaver Dam, Wisconsin, was performed in 1987-1988 to identify all residents eligible for the study.[6] Participants were examined at baseline (1988-1990) and every 5 years thereafter (1993-1995, 1998-2000, 2003-2005, 2008-2010) over a 20-

Author Affiliations: Department of Ophthalmology and Visual Sciences (Drs B.E.K. Klein and R. Klein, Mss Howard, Dreyer, and Lee); and Departments of Biostatistics and Medical Informatics and Population Health Sciences (Dr Gangnon), University of Wisconsin School of Medicine and Public Health, Madison.
Corresponding Author: Barbara E. K. Klein, MD, MPH, Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, 610 N Walnut St, Fourth Floor WARF, Madison, WI 53726-2336 (kleinb@epi.ophth.wisc.edu).

year period. All data were collected with institutional review board approval from the University of Wisconsin–Madison in conformity with all federal and state laws; the work complied with the Health Insurance Portability and Accountability Act; and the study adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from every participant at each examination.

Participants were examined at the study site, a nursing home, or their home. By design, participants were requested to be seen on or near the anniversary date of their first examination. In this way, examinations occurred at regular 5-year intervals. For all person-visits included in analyses, 86% of visits occurred within 6 months of the target visit date. The same protocols for measurements relevant to this investigation were used at each examination.[7] Participants were asked if they regularly used aspirin at least twice per week for more than 3 months. This self-report of regular aspirin use was the main exposure measure of interest in our primary analysis because it was asked at every examination. Additional information concerning frequency of aspirin use (<1 aspirin every other day, 1 every other day, 1 per day, 2 per day, 3 to 7 per day, or 8 or more per day) and dosage was obtained at the third, fourth, and fifth examinations. These data were used to calculate an estimated dose (in milligrams) per day and were used for auxiliary analyses to examine the potential dosing effect of aspirin on incidence of AMD.

Participants were asked to bring all currently used medications to the examinations. All medications, including NSAIDs and anticoagulants (eg, warfarin), were recorded. Hypertension was defined as systolic blood pressure 140 mm Hg or greater, diastolic blood pressure 90 mm Hg or greater, and/or history of blood pressure medication use. Heavy drinking was defined as consuming 4 or more servings of alcoholic beverages per day on a regular basis. A serving was defined as 12 oz (355 mL) of beer, 4 oz (118 mL) of wine, or 1.5 oz (44 mL) of liquor or distilled spirits. Blood samples were obtained and analyzed for levels of glycated hemoglobin (HbA_{1c}) and for inflammatory factors, eg, leukocyte count and C-reactive protein (CRP) level. CRP level was measured only at the baseline examination, and leukocyte count was measured at the baseline and second examinations. Diabetes was defined as self-report confirmed by use of insulin or diet to control diabetes, self-report with HbA_{1c} level greater than 6.5%, or no self-report with HbA_{1c} level greater than 7%.[8]

Photographs of the retina[7] were taken after pupillary dilation according to protocol[9] and graded in masked fashion by experienced graders using the Wisconsin Age-Related Maculopathy Grading System to assess the presence and severity of lesions associated with AMD.[9-11] Grading procedures, lesion descriptions, and detailed definitions of presence and severity appear elsewhere (eMethods, available at http://www.jama.com).[9]

The natural progression of AMD is described by the increase in level of severity. It is generally understood that an eye will have transitioned through each previous level (lower number in the scoring system) when it presents at a given severity level.

Statistical Analysis

We examined the relationship between self-reported regular aspirin use and incidence of early and late AMD in the presence of other known risk variables over 20 years of follow-up. Presence of early or late AMD was analyzed by person, combining the data from both eyes. Person-level variables were calculated at each visit for presence of early AMD, late AMD, neovascular AMD, and pure geographic atrophy. At a given visit, a person was considered free from a given type of AMD if both eyes were gradable and determined to be free of that AMD type. A person was considered to have a specific type of AMD at a given examination if at least 1 eye had gradable photographs and was determined to be prevalent of the given AMD type. If information from 1 eye was missing and the other eye was free from the given type of AMD, the person-level data were considered missing at that examination.

To be eligible for incidence of a specified type of AMD (early, late, neovascular, pure geographic atrophy), a participant must have been free of the given AMD outcome at the baseline examination and have complete AMD data from consecutive follow-up examinations, until incidence or censoring occurred. Further, to be included in analyses, a participant must have had complete data for self-reported aspirin use, age, sex, education, history of arthritis, and history of cardiovascular disease (CVD).

The 2 types of late AMD are not mutually exclusive, and both types may appear in the same eye sequentially or simultaneously. Incidence of late AMD was calculated as the first incidence of pure geographic atrophy or neovascular AMD. We followed the commonly accepted disease progression model that once a person develops neovascular AMD he or she cannot be further classified as having developed pure geographic atrophy (despite a change in the appearance of the fundus lesion); therefore, although a person who has prevalent or incident pure geographic atrophy is still at risk of developing neovascular AMD, the converse is not true. In this way, there were more persons at risk of developing neovascular AMD than any late AMD or pure geographic atrophy. Similarly, participants with early AMD were still at risk for developing late AMD; therefore, there were more participants in the risk set for late AMD than for early AMD.

For preliminary analyses, we calculated the overall percentage of participants incident for each combination of aspirin use 5 and 10 years prior to observed incidence (none at 5 years and none at 10 years, 5 years only, 10 years only, both 5 and 10 years). For each combination we then calculated the age- and sex-adjusted percentages for incidence. To explore the potential longi-

tudinal association between aspirin use and AMD, we computed hazard ratios (HRs) for incidence of early and late AMD over 20 years, with time-varying covariates updated at each examination. Because the first incident cases were observed at the second examination and the main risk factor of interest was aspirin use at baseline, we refer to this as aspirin use "5 years prior." We also considered the hypothesis that the association between aspirin use and development of AMD may not be apparent with exposure at only 5 years prior to incidence. Therefore, for this analysis we accounted for aspirin use at the examination 5 years prior to incidence as well as for aspirin use reported at the previous examination, 10 years prior to observed incidence. When examining data that included aspirin use 10 years prior to incidence, those cases incident at the first interval were not included because aspirin use 5 years prior to the baseline examination was unknown. Because of this, the total interval for the longitudinal analysis of 10-year aspirin use is 15 years.

To establish the maximally adjusted statistical models, variables potentially associated with risk of AMD were first analyzed individually in age- and sex-adjusted models. These variables included body mass index, annual income, education, diabetes, systolic and diastolic blood pressure, hypertension, history of cancer, smoking (never, past, current), ever drinking, ever heavy drinking, history of arthritis, and history of CVD. All significant factors in the age- and sex-adjusted models were then included in a maximally adjusted model. The maximally adjusted model for early AMD included age, sex, education level, ever heavy drinking, smoking, and history of arthritis. The maximally adjusted model for late AMD and its subtypes included age, age^2, sex, education, heavy drinking history, and smoking. Last, nonsignificant predictors from the maximally adjusted model were removed to establish the most parsimonious model; only these data are presented. This resulted in adjustment for age, arthritis history, and education level in models for early AMD and age, age^2, and education level in models for late AMD. Interactions between potential reasons for aspirin use (arthritis and history of CVD) and aspirin use were tested.

To assess whether the timing of visits was driven by confounding factors, visits were divided into 3 groups: early (at least 6 months before the targeted visit date [the anniversary of the baseline visit]), late (more than 6 months after the targeted visit date), and on time (within 6 months of the targeted visit date). For the sensitivity analysis, observations from early or late visits were censored. The point estimates and confidence intervals in the 2 models were consistent; therefore, the full models are presented.

To explore whether frequency of aspirin use and amount of aspirin used was associated with AMD, we examined the association between self-reported daily dose of aspirin (in milligrams) and the incidence of early and late AMD with available data from the third, fourth, and fifth examinations. We also modeled the effect of inflammatory factors (leukocyte count, interleukin-6 level, and CRP level) on the association between aspirin use and incidence of AMD. We then examined the relationship between use of any NSAID and incidence of AMD and the relationship between warfarin use and incidence of AMD.

All models presented were fit using the discrete-time hazard model using the complementary log-log link function with time-varying predictors, with *P* values representing a 2-tailed test of significance with $\alpha = .05$.[12] In this way, risk variables (eg, use of aspirin 5 and 10 years previously) were updated throughout the course of the study; the model thus captures the change in risk for incidence of AMD, and censoring is accounted for appropriately. SAS version 9.3 (SAS Institute Inc) was used for all analyses.

We also conducted a secondary, exploratory analysis to examine whether the data supported the notion that time since first report of regular aspirin use was associated with incidence of late AMD. For these models, the outcome of interest was incidence of AMD between the fourth and fifth examinations. Our exposure variable was first self-reported aspirin use 5, 10, 15, or 20 years prior to observed incidence, which was examined in 2 ways. First, we included only participants who reported using aspirin consistently at each examination following their first self-reported use or who never reported using aspirin regularly. Next, we included participants who were inconsistent in reporting regular aspirin use following their first self-report of regular aspirin use. Participants with missing aspirin use data were excluded from both of these analyses. We used logistic regression for these models, with a 2-tailed test of significance with $\alpha = .05$.

RESULTS

Of the 5924 eligible persons, 4926 aged 43 to 86 years (83%) participated in the baseline examination in 1988-1990. Ninety-nine percent of the population was white; 56% were women. The cohort was reexamined at 5-year (n=3722), 10-year (n=2962), 15-year (n=2375), and 20-year (n=1913) follow-up examinations. There was greater than 80% participation among survivors at each examination.[13-15] The mean duration of follow-up was 14.8 years, with a median duration of 15.9 years.

Participants included in these analyses tended to be younger and have fewer comorbid conditions at baseline than those excluded (TABLE 1). For incident early AMD, 2547 participants of the 4926 seen at baseline were excluded from analysis (1008 had prevalent early or late AMD at baseline, 84 were missing a covariate, 448 were missing AMD data at baseline, and 1007 did not have data at the first follow-up examination). Overall, there were 2379 participants at risk for early AMD, of which 512 developed incident disease, with a total of 6243 person-visits contributing to the analysis (FIGURE). For incidence of late AMD, 1794 participants of the 4926 seen at baseline

were excluded from analysis (74 had prevalent late AMD at baseline, 104 were missing a covariate, 407 had missing AMD data at baseline, and 1209 had missing data at the first follow-up examination). There were 3132 participants at risk for developing late AMD, of which 117 developed incident disease, with a total of 8621 person-visits included in analyses (Figure). The unadjusted incidence rate per 10 person-years was 0.164 for early AMD and 0.027 for late AMD.

There was no significant association of self-reported aspirin use 5 years prior to observed incidence of early AMD accumulated over 20 years (HR, 0.86 [95% CI, 0.71-1.05]; $P=.13$; age- and sex-adjusted incidence, 9.6% [95% CI, 8.3%-11.0%] for aspirin users vs 10.5% [95% CI, 9.5%-11.6%] for nonusers) (TABLE 2). The incidence of late AMD was greater in participants using aspirin 5 years previously than in nonusers (age- and sex-adjusted incidence, 1.4% [95% CI, 1.0%-1.9%] vs 1.0% [95% CI, 0.7%-1.4%], respectively), although the association was not significant (HR, 1.21 [95% CI, 0.84-1.74]; $P=.31$), and there was no significant association for either late AMD subtype (HR, 1.07 [95% CI, 0.68-1.67]; $P=.77$ for neovascular AMD and HR, 1.65 [95% CI, 0.91-2.99]; $P=.10$ for pure geographic atrophy) for those who reported aspirin use 5 years prior (age- and sex-adjusted incidence, 0.8% [95% CI, 0.5%-1.3%] for neovascular AMD and 0.6% [95% CI, 0.4%-1.0%] for pure geographic atrophy) vs those who did not (age- and sex-adjusted incidence, 0.7% [0.5%-1.0%] for neovascular AMD and 0.4% [0.2%-0.6%] for pure geographic atrophy) (Table 2).

Because of the possibility of a lag in effect of first reported regular use of aspirin and AMD, we examined use at both 5 and 10 years prior to observed incidence. These data were combined and modeled as a 4-level nonordinal categorical variable (TABLE 3). Only incidence analysis over 15 years can be performed because of the lack of information regarding regular aspirin use prior to the baseline examination. The overall test for association was not significant for any category of aspirin use and incident early AMD ($P=.43$), late AMD ($P=.20$), neovascular AMD ($P=.07$), and pure geographic atrophy ($P=.20$) (Table 3).

We then tested the main effects of aspirin use 5 and 10 years prior to observed incidence in this model. The main effect of aspirin use 5 years prior showed no significant association with incident early AMD (HR, 0.93 [95% CI, 0.70-1.23]; $P=.60$; age- and sex-adjusted incidence, 9.0% [95% CI, 7.6%-10.7%] for aspirin users vs 9.0% [95% CI, 7.6%-10.6%] for nonusers), late AMD (HR, 0.91 [95% CI, 0.57-1.46]; $P=.69$; age- and sex-adjusted in-

Table 1. Baseline Characteristics of the Beaver Dam Eye Study Population and Those Included in and Excluded From Analyses

Characteristic	No. (%)		
	Whole Population (N = 4926)	Included[a] (n = 3206)	Excluded[b] (n = 1720)
Age, mean (SD), y	62.0 (11.2)	59.3 (10.0)	67.2 (11.6)
Body mass index, mean (SD)[c]	28.8 (5.4)	28.8 (5.3)	28.7 (5.5)
Systolic blood pressure, mm Hg, mean (SD)	132.1 (20.5)	130.1 (19.2)	135.9 (22.2)
Sex			
Women	2762 (56.1)	1790 (55.8)	972 (56.5)
Men	2164 (43.9)	1416 (44.2)	748 (43.5)
Annual income, US$			
≤9000	760 (16.3)	354 (11.4)	406 (25.7)
10 000-19 000	1301 (27.8)	768 (24.8)	533 (33.8)
20 000-29 000	946 (20.2)	677 (21.9)	269 (17.1)
30 000-44 000	956 (20.5)	723 (23.4)	233 (14.8)
≥45 000	709 (15.2)	573 (18.5)	136 (8.6)
Education			
<High school	1440 (29.3)	719 (22.4)	721 (42.1)
High school	2134 (43.4)	1480 (46.2)	654 (38.2)
College	701 (14.2)	498 (15.5)	203 (11.8)
>College	645 (13.1)	509 (15.9)	136 (7.9)
Smoking status			
Never	2204 (44.8)	1433 (44.7)	771 (44.9)
Past	1747 (35.5)	1148 (35.8)	599 (34.9)
Current	970 (19.7)	624 (19.5)	346 (20.2)
Diabetes present			
No	4460 (91.0)	2984 (93.4)	1476 (86.5)
Yes	441 (9.0)	211 (6.6)	230 (13.5)
Hypertension present[d]			
No	2428 (49.4)	1723 (53.8)	705 (41.2)
Yes	2489 (50.6)	1482 (46.2)	1007 (58.8)
History of CVD			
No	4124 (84.9)	2843 (89.3)	1281 (76.6)
Yes	731 (15.1)	339 (10.7)	392 (23.4)
History of heavy drinking[e]			
No	4068 (82.8)	2677 (83.6)	1391 (81.4)
Yes	844 (17.2)	526 (16.4)	318 (18.6)
Using aspirin			
No	3816 (77.6)	2513 (78.4)	1303 (76.2)
Yes	1101 (22.4)	693 (21.6)	408 (23.8)

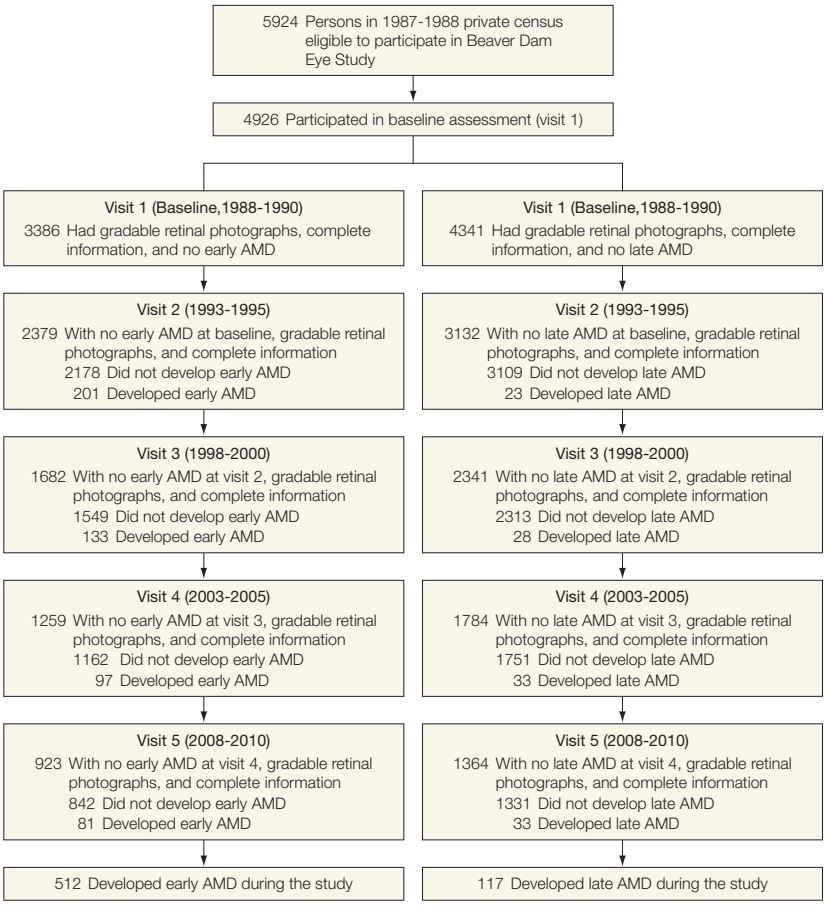
Abbreviations: AMD, age-related macular degeneration; CVD, cardiovascular disease.
[a] Participant data included in 1 or more analyses (incidence of early AMD, late AMD, neovascular AMD, and/or pure geographic atrophy).
[b] Participant data excluded from all analyses.
[c] Calculated as weight in kilograms divided by height in meters squared.
[d] Defined as systolic blood pressure 140 mm Hg or greater, diastolic blood pressure 90 mm Hg or greater, and/or use of antihypertensive medication.
[e] Defined as consuming 4 or more servings of alcoholic beverages per day on a regular basis. A serving was defined as 12 oz (355 mL) of beer, 4 oz (118 mL) of wine, or 1.5 oz (44 mL) of liquor or distilled spirits.

cidence, 1.3% [95% CI, 0.9%-1.9%] for users vs 1.4% [95% CI, 1.9%-2.1%] for nonusers), neovascular AMD (HR, 0.66 [95% CI, 0.37-1.19]; *P*=.17; age- and sex-adjusted incidence, 0.8% [95% CI, 0.5%-1.3%] for users vs 1.1% [95% CI, 0.7%-1.6%] for nonusers), or pure geographic atrophy (HR, 2.25 [95% CI, 0.75-6.72]; *P*=.15; age- and sex-adjusted incidence, 0.6% [95% CI, 0.4%-1.1%] for users vs 0.4% [95% CI, 0.2%-0.8%] for nonusers).

The main effect of aspirin use 10 years prior was significant for predicting the incidence of late AMD (HR, 1.63 [95% CI, 1.01-2.63]; *P*=.045; age- and sex-adjusted incidence, 1.8% [95% CI, 1.2%-2.6%] for users vs 1.0% [95% CI, 0.7%-1.5%] for nonusers). When examining the relationships by late AMD subtype, neovascular AMD was significantly associated with such use (HR, 2.20 [95% CI, 1.20-4.15]; *P*=.01; age- and sex-adjusted incidence, 1.4% [95% CI, 0.9%-2.1%] for users vs 0.6% [95% CI, 0.4%-1.0%] for nonusers), but pure geographic atrophy was not (HR, 0.66 [95% CI, 0.25-1.95]; *P*=.46; age- and sex-adjusted incidence, 0.5% [95% CI, 0.3%-1.0%] for users vs 0.5% [95% CI, 0.3%-0.9%] for nonusers). Similar analyses for the incidence of early AMD showed no significant associations with use of aspirin 10 years prior (HR, 0.86 [95% CI, 0.65-1.13]; *P*=.28; age- and sex-adjusted incidence, 8.5% [95% CI, 6.9%-10.5%] for users vs 9.5% [95% CI, 8.3%-10.9%] for nonusers).

History of arthritis and CVD, 2 common reasons for aspirin use, were analyzed to investigate the possibility of confounding by indication. For predicting incidence of early AMD, no significant interactions were found

Figure. Numbers of Participants at Each Phase of the Beaver Dam Eye Study Included in Analyses of Incidence of Early and Late Age-Related Macular Degeneration



Complete information includes complete data on self-reported use of aspirin, age, education, and (for early age-related macular degeneration [AMD]) history of arthritis.

Table 2. Relationships of Incidence of Age-Related Macular Degeneration Outcomes With Self-reported Regular Aspirin Use 5 Years Prior to Observed Incidence Over 20 Years

Incident AMD Outcome	Using Aspirin 5 y Prior to Incidence	Person-Visits		Age- and Sex-Adjusted Incidence (95% CI), %	HR (95% CI)	*P* Value
		No. at Risk	Incident Cases, No.			
Early AMD[a]	No	4398	348	10.5 (9.5-11.6)	1 [Reference]	.13
	Yes	1845	164	9.6 (8.3-11.0)	0.86 (0.71-1.05)	
Any late AMD[b]	No	5957	62	1.0 (0.7-1.4)	1 [Reference]	.31
	Yes	2664	55	1.4 (1.0-1.9)	1.21 (0.84-1.74)	
Neovascular AMD[b]	No	5994	44	0.7 (0.5-1.0)	1 [Reference]	.77
	Yes	2681	34	0.8 (0.5-1.3)	1.07 (0.68-1.67)	
Pure geographic atrophy[b]	No	5915	20	0.4 (0.2-0.6)	1 [Reference]	.10
	Yes	2633	24	0.60 (0.4-1.0)	1.65 (0.91-2.99)	

Abbreviations: AMD, age-related macular degeneration; HR, hazard ratio.
[a] Adjusted for age, arthritis history, and education level.
[b] Adjusted for age, age^2, and education level.

Table 3. Relationships of Incidence of Age-Related Macular Degeneration Outcomes With Self-reported Regular Use of Aspirin 5 and 10 Years Prior to Observed Incidence Over 15 Years

	Person-Visits					
	No. at Risk for Outcome	Incident Cases, No.	Age- and Sex-Adjusted Incidence (95% CI), %	HR (95% CI)	*P* Value	Overall *P* Value
Early AMD[a]						
Aspirin use						
No use 5 or 10 y prior	2254	170	9.3 (8.1-10.7)	1 [Reference]		
Use 5 y prior, no use 10 y prior	644	60	10.0 (7.9-12.6)	1.03 (0.77-1.38)	.85	.43
No use 5 y prior, use 10 y prior	277	24	9.6 (6.7-13.7)	0.95 (0.63-1.45)	.83	
Use 5 and 10 y prior	686	57	8.1 (6.3-10.4)	0.79 (0.58-1.09)	.15	
Test of main effects						
Use vs no use 5 y prior						
No use	2531	194	9.0 (7.6-10.6)	1 [Reference]	.60	
Use	1330	117	9.0 (7.6-10.7)	0.93 (0.70-1.23)		
Use vs no use 10 y prior						
No use	2898	230	9.5 (8.3-10.9)	1 [Reference]	.28	
Use	963	81	8.5 (6.9-10.5)	0.86 (0.65-1.13)		
Any late AMD[b]						
Aspirin use						
No use 5 or 10 y prior	3091	38	1.1 (0.7-1.7)	1 [Reference]		
Use 5 y prior, no use 10 y prior	948	13	0.9 (0.5-1.6)	0.81 (0.44-1.52)	.52	.20
No use 5 y prior, use 10 y prior	401	10	1.7 (0.9-3.1)	1.46 (0.73-2.91)	.29	
Use 5 and 10 y prior	1045	33	1.8 (1.1-2.7)	1.48 (0.93-2.37)	.10	
Test of main effects						
Use vs no use 5 y prior						
No use	3492	48	1.4 (0.9-2.1)	1 [Reference]	.69	
Use	1993	46	1.3 (0.9-1.9)	0.91 (0.57-1.46)		
Use vs no use 10 y prior						
No use	4039	51	1.0 (0.7-1.5)	1 [Reference]	.05	
Use	1446	43	1.8 (1.2-2.6)	1.63 (1.01-2.63)		
Neovascular AMD[b]						
Aspirin use						
No use 5 or 10 y prior	3111	25	0.7 (0.5-1.2)	1 [Reference]		
Use 5 y prior, no use 10 y prior	954	6	0.4 (0.2-1.1)	0.58 (0.24-1.40)	.23	.07
No use 5 y prior, use 10 y prior	408	9	1.5 (0.7-2.9)	1.92 (0.89-4.13)	.10	
Use 5 and 10 y prior	1054	21	1.2 (0.7-2.0)	1.46 (0.81-2.60)	.21	
Test of main effects						
Use vs no use 5 y prior						
No use	3519	34	1.1 (0.7-1.6)	1 [Reference]	.17	
Use	2008	27	0.8 (0.5-1.3)	0.66 (0.37-1.19)		
Use vs no use 10 y prior						
No use	4065	31	0.6 (0.4-1.0)	1 [Reference]	.01	
Use	1462	30	1.4 (0.9-2.1)	2.20 (1.20-4.15)		
Pure geographic atrophy[b]						
Aspirin use						
No use 5 or 10 y prior	3068	15	0.5 (0.2-0.9)	1 [Reference]		
Use 5 y prior, no use 10 y prior	943	8	0.6 (0.3-1.2)	1.26 (0.54-2.94)	.60	.20
No use 5 y prior, use 10 y prior	392	1	0.2 (0.0-1.3)	0.37 (0.05-2.66)	.32	
Use 5 and 10 y prior	1025	13	0.7 (0.3-1.3)	1.49 (0.71-3.12)	.29	
Test of main effects						
Use vs no use 5 y prior						
No use	3460	16	0.4 (0.2-0.8)	1 [Reference]	.15	
Use	1968	21	0.6 (0.4-1.1)	2.25 (0.75-6.72)		
Use vs no use 10 y prior						
No use	4011	23	0.5 (0.3-0.9)	1 [Reference]	.45	
Use	1417	14	0.5 (0.3-1.0)	0.66 (0.25-1.95)		

Abbreviations: AMD, age-related macular degeneration; HR, hazard ratio.
[a] Adjusted for age, arthritis history, and education level.
[b] Adjusted for age, age^2, and education level.

Table 4. Relationship of Age-Related Macular Degeneration Outcomes to Aspirin Exposure Patterns Prior to the Incidence of Age-Related Macular Degeneration

	Unadjusted		Age- and Sex-Adjusted			
AMD Outcome and Aspirin Exposure Pattern	No. at Risk	Incident Cases, No.	Incidence (95% CI), %	OR (95% CI)	*P* Value	Overall *P* value
Early AMD						
First consistent exposure						
None	403	40	9.4 (6.8-12.8)	1 [Reference]		
5 y prior	169	21	11.7 (7.6-17.5)	1.28 (0.72-2.26)	.41	
10 y prior	164	12	6.3 (3.5-11.0)	0.65 (0.33-1.29)	.22	.52
15 y prior	61	8	9.5 (4.6-18.6)	1.01 (0.44-2.33)	.98	
20 y prior	64	7	8.9 (4.1-18.0)	0.94 (0.39-2.26)	.89	
None or at visit 4 only	572	61	10.1 (7.8-13.0)	1 [Reference]	.22	
10, 15, or 20 y prior	289	27	7.6 (5.1-11.2)	0.73 (0.45-1.20)		
First exposure[a]						
None	403	40	9.6 (6.8-12.7)	1 [Reference]		
5 y prior	169	21	11.7 (7.7-17.5)	1.29 (0.73-2.29)	.39	
10 y prior	199	15	6.6 (4.0-10.9)	0.69 (0.37-1.30)	.25	.48
15 y prior	115	14	9.3 (5.4-15.6)	1.00 (0.51-1.94)	.99	
20 y prior	175	22	10.6 (6.9-15.9)	1.15 (0.65-2.04)	.63	
None or at visit 4 only	572	61	10.1 (7.8-12.9)	1 [Reference]	.44	
10, 15, or 20 y prior	489	51	8.7 (6.5-11.6)	0.85 (0.57-1.28)		
Any late AMD						
First consistent exposure						
None	514	9	1.1 (0.5-2.3)	1 [Reference]		
5 y prior	215	3	0.9 (0.3-2.8)	0.81 (0.21-3.09)	.76	
10 y prior	214	10	2.1 (1.0-4.7)	2.02 (0.77-5.30)	.15	.53
15 y prior	95	4	1.5 (0.5-4.5)	1.38 (0.40-4.79)	.62	
20 y prior	98	5	2.0 (0.7-5.6)	1.85 (0.56-6.08)	.31	
None or at visit 4 only	729	12	1.0 (0.5-2.0)	1 [Reference]	.10	
10, 15, or 20 y prior	407	19	1.9 (1.0-3.8)	1.91 (0.88-4.14)		
First exposure[a]						
None	514	9	1.1 (0.5-2.3)	1 [Reference]		
5 y prior	215	3	0.9 (0.3-2.9)	0.81 (0.21-3.09)	.76	
10 y prior	268	10	1.6 (0.8-3.8)	1.62 (0.63-4.20)	.32	.64
15 y prior	170	9	1.9 (0.8-4.4)	1.79 (0.67-4.80)	.25	
20 y prior	249	7	1.2 (0.5-2.9)	1.11 (0.40-3.12)	.84	
None or at visit 4 only	729	12	1.0 (0.5-2.0)	1 [Reference]	.22	
10, 15, or 20 y prior	687	26	1.6 (0.9-2.9)	1.57 (0.76-3.23)		
Neovascular AMD						
First consistent exposure						
None	518	6	0.8 (0.3-1.8)	1 [Reference]		
5 y prior	217	1	0.3 (0.0-2.2)	0.41 (0.05-3.45)	.41	
10 y prior	214	8	1.9 (0.8-4.4)	2.52 (0.83-7.63)	.10	.14
15 y prior	98	4	1.6 (0.5-4.9)	2.09 (0.56-7.88)	.28	
20 y prior	100	5	2.1 (0.7-6.1)	2.87 (0.80-10.37)	.11	
None or at visit 4 only	735	7	0.6 (0.3-1.4)	1 [Reference]	.02	
10, 15, or 20 y prior	412	17	1.8 (0.9-3.8)	2.99 (1.18-7.57)		
First exposure[a]						
None	518	6	0.8 (0.3-1.9)	1 [Reference]		
5 y prior	217	1	0.3 (0.0-2.3)	0.41 (0.05-3.44)	.41	
10 y prior	269	8	1.5 (0.7-3.5)	1.99 (0.66-5.97)	.22	.23
15 y prior	175	8	1.8 (0.8-4.4)	2.41 (0.79-7.32)	.12	
20 y prior	254	7	1.3 (0.5-3.1)	1.69 (0.55-5.24)	.36	
None or at visit 4 only	735	7	0.6 (0.3-1.4)	1 [Reference]	.05	
10, 15, or 20 y prior	698	23	1.5 (0.8-2.8)	2.41 (1.00-5.81)		

(continued)

Table 4. Relationship of Age-Related Macular Degeneration Outcomes to Aspirin Exposure Patterns Prior to the Incidence of Age-Related Macular Degeneration (continued)

	Unadjusted		Age- and Sex-Adjusted			
AMD Outcome and Aspirin Exposure Pattern	No. at Risk	Incident Cases, No.	Incidence (95% CI), %	OR (95% CI)	*P* Value	Overall *P* value
Pure geographic atrophy[b]						
First consistent exposure						
None	508	3	0.3 (0.1-1.2)			
5 y prior	214	2	0.5 (0.1-2.4)			
10 y prior	206	2	0.3 (0.1-2.0)			
15 y prior	92	1	0.3 (0.0-2.8)			
20 y prior	93	0				
None or at visit 4 only	722	5	0.3 (0.1-1.2)			
10, 15, or 20 y prior	391	3	0.2 (0.1-1.2)			
First exposure[a]						
None	508	3	0.3 (0.1-1.3)			
5 y prior	214	2	0.5 (0.1-2.5)			
10 y prior	260	2	0.3 (0.1-1.6)			
15 y prior	163	2	0.6 (0.1-2.0)			
20 y prior	243	1	0.2 (0.0-1.3)			
None or at visit 4 only	722	5	0.4 (0.1-1.2)	1 [Reference]	.57	
10, 15, or 20 y prior	666	5	0.3 (0.1-1.0)	0.69 (0.19-2.50)		

Abbreviations: AMD, age-related macular degeneration; NA, not available; OR, odds ratio.
[a] Includes participants with inconsistent aspirin exposure (participant reported aspirin use, followed by reporting no aspirin use at a later examination). This category does not include participants with reported aspirin use followed by missing aspirin use data.
[b] OR and *P* value data cannot be estimated because of very low incidence.

between arthritis or CVD and aspirin use 5 years prior to incidence (*P*=.16 for arthritis, *P*=.45 for CVD) or 5 and 10 years prior (*P*=.64 for arthritis, *P*=.33 for CVD). Similarly, for predicting incidence of any form of late AMD, no significant interactions were found between aspirin use 5 years prior and history of arthritis (*P*=.28) or CVD (*P*=.62) or between aspirin use 5 and 10 years prior and history of arthritis (*P*=.16) or CVD (*P*=.43).

Milligrams of aspirin taken per day were calculated for the third, fourth, and fifth examination phases. No significant relationship was found between milligrams of aspirin per day taken 5 years prior to observed early AMD (*P*=.53) or late AMD (*P*=.22). Similarly, no significant relationship was found between milligrams of aspirin reported taken 5 and 10 years prior and observed incidence of early AMD (*P*=.27) or late AMD (*P*=.37).

We examined whether the association between aspirin use and incidence of neovascular AMD was related to use of any NSAID and found no relationship between the use of any NSAID 10 years prior and incidence of neovascular AMD (*P*=.33). We also investigated whether warfarin was associated with incidence of late AMD or its subtypes and found no associations between AMD and warfarin use 5 years prior (*P*=.56 for late AMD; *P*=.88 for neovascular AMD; *P*=.52 for pure geographic atrophy) or 10 years prior (*P*=.15 for late AMD; *P* value nonestimable for neovascular AMD; *P*=.89 for pure geographic atrophy) to observed incidence.

To examine possible effects of systemic inflammation and the possible protective role of aspirin in the presence of systemic inflammation, we examined the associations of leukocyte count and CRP level with incidence of AMD and the effects of these inflammatory factors on the relationship between aspirin use reported 5 years prior and incident AMD. Neither were associated with incidence of early AMD (*P*=.13 for leukocyte count; *P*=.21 for CRP level) or late AMD (*P*=.56 for leukocyte count; *P*=.29 for CRP level), and neither showed a significant interaction with aspirin use (early AMD: *P*=.87 for leukocyte count and *P*=.29 for CRP level; late AMD: *P*=.25 for leukocyte count and *P*=.07 for CRP level). Adjusting for leukocyte count and CRP level did not alter the associations seen between aspirin use and incident late AMD.

To further explore the finding that time of first reported regular aspirin use was associated with AMD, we examined the data on aspirin use only in participants who had complete information on self-reported aspirin use at all study visits from the baseline visit through the fourth visit, who were free from AMD at the fourth visit, and who had complete outcome information from the most recent visit (TABLE 4). There was no apparent relationship between the visit since first regular use of aspirin and incidence of early AMD. Results are similar for those with consistent and inconsistent use.

For any late AMD, participants with no aspirin use and those with aspirin use only at the visit prior to the inci-

dence of late AMD (use at the fourth visit) had a similar incidence (1.75% and 1.40%, respectively). Those who had reported regular aspirin use 10, 15, or 20 years prior to observed incidence showed a higher incidence than those with no aspirin use or only recent aspirin use (5 years prior to observed incidence). Incidence was similar for 10 years (4.67%), 15 years (4.21%), and 20 years (5.10%) since aspirin use was first consistently reported. The results are similar for participants with inconsistent use. It should be noted that for late AMD, several cells contain very low counts for incident cases (Table 4).

For pure geographic atrophy, there was no discernible pattern between incidence and years since first self-reported aspirin use. For neovascular AMD, the pattern was similar to what was seen for incidence of any late AMD (Table 4).

COMMENT

In our study, aspirin use 10 years prior was associated with incidence of neovascular AMD. Our exploratory analyses tend to support the findings of our primary analysis. Our hazard ratio estimate for neovascular AMD in participants who reported regular use of aspirin 10 years prior to observed AMD was 2.20 (95% CI, 1.20-4.15) (Table 3). This is based on our modeling of specific potential risk factors in a Midwestern, primarily white population. Although it is possible to estimate an attributable risk, the number of incident cases that our estimate is based on was small and requires corroboration before developing risk algorithms for clinical use.

Adjusting for age, age^2, education level, and aspirin use 5 years prior to observed incidence, the adjusted attributable risk of late AMD for aspirin use 10 years prior to observed incidence was 0.77%, with an adjusted attributable risk fraction of 53.2%.[16] This is in keeping with the finding of a small but significant cross-sectional association between aspirin use and AMD in the European Eye study and the inference that for a patient, aspirin use for cardioprevention does not imply a great increase in risk of AMD.[17,18] If our finding is borne out in other studies, it suggests that the effect of aspirin on mechanisms leading to AMD may be different, at least partially, from aspirin's immediate effects on clotting, which seem to be responsible for cardioprotection.[19] Not all retinal lesions characterizing neovascular AMD involve bleeding that is detectable in photography. Aspirin, aside from its effects on clotting, may enhance choroidal neovascularization.[20] Aspirin has been shown to increase vascular density in a laboratory model.[21] Thus, it is possible that in the presence of injury, aspirin encourages the growth of aberrant new vessels.

Two studies by Christen and colleagues[22,23] describing the experience in 2 large randomized controlled trials for prevention of CVD, one with 7-year follow-up and the other with 10-year follow-up, found no evidence of a direct association between use of low-dose aspirin and late lesions of AMD. Those studies were performed among health professionals who are likely to be more health conscious than general populations. The number of AMD cases was small in both studies, and the definition and method of classification of the end point differed from the current study and the European Eye Study,[17] which both used photographic documentation and systematic grading of lesions as opposed to self-reported AMD with decreased vision confirmed by medical record. Thus, there are likely to be important differences in exposures and outcomes and ascertainment between the studies that may have caused the disparate findings.

Several limitations may have affected our findings. First, there was a lack of detailed information on aspirin exposure at some visits. When the study began, questions on frequency of use and dosage were not initially included but were added into subsequent examinations to accommodate important clinical therapeutic trends in the community, especially the increasing use of aspirin for CVD. Second, leukocyte count was only measured at the baseline and second examinations; therefore, we could not evaluate potential associations for every study interval. Similar limitations apply to CRP measurements, which might have informed our analysis regarding possible effects of systemic inflammation and its potentially modifying effect on the association of AMD with aspirin use. Third, the study population is almost entirely white of European ancestry, so the extent to which our results may generalize to other races/ethnicities, particularly groups at elevated risk for CVD, is unknown.

Our findings are consistent with a small but statistically significant association between regular aspirin use and incidence of neovascular AMD. Additional replication is required to confirm our observations. If confirmed, defining the causal mechanisms may be important in developing methods to block this effect to prevent or retard the development of neovascular AMD in persons who use aspirin, especially to prevent CVD.

Author Contributions: Dr B. E. K. Klein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: B. E. K. Klein, R. Klein.
Acquisition of data: B. E. K. Klein, Dreyer, R. Klein.
Analysis and interpretation of data: B. E. K. Klein, Howard, Gangnon, Lee.
Drafting of the manuscript: B. E. K. Klein, Howard.
Critical revision of the manuscript for important intellectual content: B. E. K. Klein, Howard, Gangnon, Dreyer, Lee, R. Klein.
Statistical analysis: Howard, Gangnon, Lee.
Obtained funding: B. E. K. Klein, R. Klein.
Administrative, technical, or material support: B. E. K. Klein, Dreyer, R. Klein.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr R. Klein reported serving as a consultant to Pfizer. No other authors reported disclosures.
Funding/Support: This study was supported by National Institutes of Health (NIH) grant EY06594 (Drs B. E. K. Klein, R. Klein). The National Eye Institute provided funding for the entire study, including for collection and analyses of data. Additional support was provided by Senior Scientific Investigator Awards from Research to Prevent Blindness (Drs B. E. K. Klein, R. Klein).
Role of the Sponsor: The funding organizations had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.
Disclaimer: The content of this article is solely the re-

sponsibility of the authors and does not necessarily reflect the official views of the National Eye Institute or the NIH.

Additional Contributions: Heidi M. G. Christian, BA, and Mary Kay Aprison, BS, of the Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, assisted with technical editing and preparation of the manuscript. They received no additional compensation beyond their normal wages as employees of the University of Wisconsin for their assistance.

Online-Only Material: The eMethods are available at http://www.jama.com.

REFERENCES

1. Soni A. Aspirin Use Among the Adult U.S. Noninstitutionalized Population, With and Without Indicators of Heart Disease, 2005. Rockville, MD: Agency for Healthcare Research and Quality; 2007. Statistical Brief 179.

2. US Food and Drug Administration (FDA). Aspirin: Questions and Answers. FDA website. http://www.fda.gov/drugs/resourcesforyou/consumers/questionsanswers/ucm071879.htm. Accessed January 17, 2012.

3. el Baba F, Jarrett WH II, Harbin TS Jr, et al. Massive hemorrhage complicating age-related macular degeneration: clinicopathologic correlation and role of anticoagulants. *Ophthalmology*. 1986;93(12):1581-1592.

4. Kiernan DF, Hariprasad SM, Rusu IM, Mehta SV, Mieler WF, Jager RD. Epidemiology of the association between anticoagulants and intraocular hemorrhage in patients with neovascular age-related macular degeneration. *Retina*. 2010;30(10):1573-1578.

5. Tilanus MA, Vaandrager W, Cuypers MH, Verbeek AM, Hoyng CB. Relationship between anticoagulant medication and massive intraocular hemorrhage in age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol*. 2000;238(6):482-485.

6. Klein R, Klein BE, Linton KL, De Mets DL. The Beaver Dam Eye Study: visual acuity. *Ophthalmology*. 1991;98(8):1310-1315.

7. Klein R, Davis MD, Magli YL, Segal P, Klein BE, Hubbard L. The Wisconsin Age-Related Maculopathy Grading System. *Ophthalmology*. 1991;98(7):1128-1134.

8. Sahakyan K, Lee KE, Shankar A, Klein R. Serum cystatin C and the incidence of type 2 diabetes mellitus. *Diabetologia*. 2011;54(6):1335-1340.

9. Klein BE, Klein R, Linton KL, Magli YL, Neider MW. Assessment of cataracts from photographs in the Beaver Dam Eye Study. *Ophthalmology*. 1990;97(11):1428-1433.

10. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 1992;99(6):933-943.

11. Klein R, Klein BE, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 1997;104(1):7-21.

12. Singer JD, Willett JB. *Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence.* Oxford, United Kingdom: Oxford University Press; 2003:407-467.

13. Klein R, Klein BE, Lee KE. Changes in visual acuity in a population: the Beaver Dam Eye Study. *Ophthalmology*. 1996;103(8):1169-1178.

14. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Chappell RJ. Changes in visual acuity in a population over a 10-year period: the Beaver Dam Eye Study. *Ophthalmology*. 2001;108(10):1757-1766.

15. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Gangnon RE. Changes in visual acuity in a population over a 15-year period: the Beaver Dam Eye Study. *Am J Ophthalmol*. 2006;142(4):539-549.

16. Greenland S. Model-based estimation of relative risks and other epidemiologic measures in studies of common outcomes and in case-control studies. *Am J Epidemiol*. 2004;160(4):301-305.

17. de Jong PT, Chakravarthy U, Rahu M, et al. Associations between aspirin use and aging macula disorder: the European Eye Study. *Ophthalmology*. 2012;119(1):112-118.

18. Scheck A. Daily Aspirin Use Associated With AMD. American Academy of Ophthalmology website. http://www.aao.org/publications/eyenet/201201/news.cfm#two. Accessed September 12, 2012.

19. Ridker PM, Manson JE, Buring JE, Goldhaber SZ, Hennekens CH. The effect of chronic platelet inhibition with low-dose aspirin on atherosclerotic progression and acute thrombosis: clinical evidence from the Physicians' Health Study. *Am Heart J*. 1991;122(6):1588-1592.

20. Battinelli EM, Markens BA, Italiano JE Jr. Release of angiogenesis regulatory proteins from platelet alpha granules: modulation of physiologic and pathologic angiogenesis. *Blood*. 2011;118(5):1359-1369.

21. Goertz O, Ring A, Buschhaus B, et al. Influence of anti-inflammatory and vasoactive drugs on microcirculation and angiogenesis after burn in mice. *Burns*. 2011;37(4):656-664.

22. Christen WG, Glynn RJ, Ajani UA, et al. Age-related maculopathy in a randomized trial of low-dose aspirin among US physicians. *Arch Ophthalmol*. 2001;119(8):1143-1149.

23. Christen WG, Glynn RJ, Chew EY, Buring JE. Low-dose aspirin and medical record–confirmed age-related macular degeneration in a randomized trial of women. *Ophthalmology*. 2009;116(12):2386-2392.